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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,807	09/19/2001	Si Lok	98-17C1	1783

7590

08/12/2003

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EXAMINER

O HARA, EILEEN B

ART UNIT

PAPER NUMBER

1646

DATE MAILED: 08/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Applicant(s)

09/955,807

Applicant(s)

LOK ET AL.

Examiner

Eileen O'Hara

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 22 May 2003.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 3-19 is/are pending in the application.
- 4a) Of the above claim(s) 3-7 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 8-19 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☒ Claim(s) 3-19 ^{are} subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

DETAILED ACTION

1. Claims 3-19 are pending in the instant application. Claims 1 and 2 have been canceled and claims 8-19 have been added as requested by Applicant in Paper Number 8, filed May 22, 2003.

Election/Restrictions

2. Applicant's election without traverse of Group I, drawn to polypeptides of SEQ ID NO: 2 in Paper No. 8 is acknowledged.

Claims 3-7 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 8-19 are currently under examination.

Priority

3. The current status (abandoned) of parent application 09/410,603 should be updated in the first sentence of the specification.

Claim Objections

4. Applicant is advised that should claims 9-13 are be found allowable, claims 15-19 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Claim Rejections - 35 USC § 101 and § 112

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claims 8-19 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility. Claims 8-19 are directed to the protein of SEQ ID NO: 2, identified as Secretory Protein-48 (Zsig48). The instant specification discloses that Zsig48 is a 105 amino acid protein, which is asserted to be a cytokine, however, the protein (or encoding nucleic acids) do not have any specific and substantial utility, or a well established utility, as determined according to the current Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday, January 5, 2001.

The claims are directed to isolated polypeptide comprising an amino acid sequence having at least 95% identity with amino acid residues 41-105 of SEQ ID NO: 2, or polypeptides comprising amino acids 29-105, 27-105, 26-105, or the entire sequence of SEQ ID NO: 2. The amino acid sequences comprising less than the full-length protein are alternative forms of the mature sequence lacking the signal sequence. The specification on page 24 suggests that due to the structure of Zsig48, it may be a peptide ligand for the G-protein coupled 7-transmembrane domain class of receptors, and that Zsig48 is highly expressed in the heart, placenta and kidney, and that Zsig48 is also expressed in leukocytes by RT-PCR (page 25). The specification contains numerous implied or asserted utilities for the polypeptide and encoding nucleic acid and associated antibodies, such as use as hybridization probes, in chromosome and gene mapping, to

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identify molecules that bind to the protein (including agonists and antagonists), to make “knock-out” mice or other animals, in gene therapy, therapeutic agents, and for the production of antibodies. The utilities that pertain solely to nucleic acids (e.g. hybridization, chromosome and gene mapping, anti-sense) would not convey to the encoded protein. With respect to the remaining utilities, none of these asserted utilities is specific for the disclosed Zsig48 protein, as each of the aforementioned utilities could be asserted for any naturally occurring protein, and further, as none of the asserted utilities requires any feature or activity that is specific to the disclosed, and there is no disease or disorder that has been correlated with the protein or encoding nucleic acids, so that methods of diagnosis or therapy are not specific and substantial.

The specification asserts that the Zsig48 polypeptides cause leukocytes to proliferate and thus can be used to elevate leukocytes in cancer treatments and in immunosuppressed patients, and describes an experiment on pages 117-120 (Example 3) in which the effect of Zsig48 on peripheral blood leukocytes in a mixed leukocyte reaction was tested. Example 3 of the specification is stimulatory activity in a mixed and in an unmixed lymphocyte reaction (MLR) assay. However, the ability of a protein to stimulate lymphocyte proliferation in this assay does not support a specific and substantial utility for the claimed invention. The ability to stimulate or inhibit lymphocyte proliferation in the MLR assay is an artificial *in vitro* system and does not provide for what specific conditions or for which specific diseases the claimed invention would predictably function. The assertion that the claimed invention could be useful for the treatment of conditions where the enhancement of the immune response would be beneficial (abstract) is not specific since there are many such conditions, and it is not predictable of which conditions the claimed invention may function, if any.

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Mixed lymphocyte culture (MLC) is a special case of antigen stimulation in which T lymphocytes respond to foreign histocompatibility antigen on unrelated lymphocytes or monocytes. MLC is a functional assay of cellular response to stimulatory determinants associated predominantly with HLA class II molecules. A single genetic locus or region, known as HLA, controls the MLC reactivity. The MLC assay recognizes disparate HLA class II molecules and the resulting T-cell activation, which is thought to represent an *in vitro* model of the afferent arm of the *in vivo* allograft reaction. The degree of reactivity observed correlates with the degree of antigenic disparity between responding and stimulating cells. Briefly, when the lymphocytes of 2 HLA-disparate individuals are combined in tissue culture, the cells enlarge, synthesize DNA, and proliferate, whereas HLA-identical cells remain quiescent. Since both cells will normally proliferate, a one way test is used to monitor the response of a single responder cell by inactivating the stimulator cell by radiation or drugs in order to inhibit DNA synthesis of the stimulator cell. The proliferation is driven primarily by the differences in the class II HLA antigens between the 2 test cells (or individuals). This reaction is not predictive of general responses of the immune system because, *in vivo*, activation of a lymphocyte is controlled not only by antigen binding but also by interactions with other cells. All T cells must cooperate with antigen-presenting cells, whereas B cells and cytotoxic T cells depend on helper T lymphocytes. These interactions either require direct surface-to surface contact or are mediated by cytokines that act only over extremely short distances. Because of this interdependence, lymphocyte activation occurs commonly and efficiently in the secondary lymphoid organs, where lymphocytes, antigens, and antigen-presenting cells encounter one another at close quarters. See pages 30-31, 208-209, 246-247 of "Basic and Clinical

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Immunology,” 1994. See also, “Manual of Clinical Laboratory Immunology,” 6th Edition at pages 1164-1166.

Kahan (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2) clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy; there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions. Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result *in vitro* does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. Therefore, the MLC assay, which is art recognized for determining histocompatibility, does not appear to be predictive of general immune responses *in vivo*.

Additionally, difficulties arise in quantification when using MLC as a test for T cell function due to variations in stimulator cell antigens that determine the degree of genetic disparity between stimulator and responder cells. MLC is typically used for determining histocompatibility in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders. Although an autologous control combining self with irradiated self was performed to normalize the response of each cell to stimulators, there is known inherent variability of individual cellular responses from day to day which requires performing the entire familial MLC at one time in the case of determining histocompatibility for transplantation (page

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246 in "Basic and Clinical Immunology"). When performing the MLC assay, each individual lot of a serum source should be screened for growth support capabilities and possible HLA antibodies (see page 1165 in "Manual of Clinical Laboratory Immunology"). Additionally, the screen should include a control response to a pool of allogeneic cells to measure maximum response and an autologous control to ensure low backgrounds.

Therefore, the MLC (a.k.a. MLR) assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to stimulate proliferation in the MLC assay may not be a general stimulus to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out above, there are several controls which the art recognizes as being essential for meaningful results for this assay, including a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. In conclusion, the results of the MLC (a.k.a. MLR) assay do not support a specific and substantial utility for the claimed invention because the assay is not predictive of immune response in general, and one of ordinary skill in the art would not

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expect a stimulatory effect in the MLC assay to correlate to a general stimulatory effect on the immune system, absent evidence to the contrary. Thus, the data do not support the assertion that the Zsig48 polypeptide can be used to promote proliferation of leukocytes. Significant further research would have been required of the skilled artisan to determine whether Zsig48 can stimulate proliferation of leukocytes, and thus the asserted utility is not substantial.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 8-19 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Even if the specification were enabling of how to use the polypeptide of SEQ ID NO: 2, enablement would not be found commensurate in scope with the claims. Even if there were a patentable use for the protein of SEQ ID NO: 2, variants of 95% identity would not be enabled because the specification has not taught one of ordinary skill in the art how to use them. Since the MLR assay discussed above is not predictive of the Zsig48 polypeptide having leukocyte proliferation activity, this is not a specific functional limitation of claim 8, and the specification has not provided guidance on how to make and use a polypeptide comprising an amino acid sequence having at least 95% identity with amino acids 41-105 of SEQ ID NO: 2 without undue experimentation. There are no motifs identified that are critical to function, there is a lack of knowledge in the prior art of a relationship between Zsig48 and

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related proteins, it is not predictable how any given set of amino acid changes will affect the protein's activity.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 12, 13, 18 and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12, 13, 18 and 19 are indefinite because they recite "wherein the polypeptide comprises (or consists of) *an* amino acid sequence of SEQ ID NO: 2", so it is not clear if it is the entire amino acid sequence that is being claimed, or a smaller portion. The rejection would be withdrawn by replacing "an" with "the".

Effective Priority Date

35 U.S.C. § 119(e) states that:

An application for patent filed under section 111(a) or section 363 of this title for an invention disclosed in the manner provided by the first paragraph of section 112 of this title in a provisional application filed under section 111(b) of this title, by an inventor or inventors named in the provisional application, shall have the same effect, as to such invention, as though filed on the date of the provisional application filed under section 111(b) of this title, if the application for patent filed under section 111(a) or section 363 of this title is filed not later than 12 months after the date on which the provisional application was filed and if it contains or is amended to contain a specific reference to the provisional application.

7. Applicant is advised that the instant application can only receive benefit under 35 U.S.C. § 119(e) from an earlier application which meets the requirements of 35 U.S.C. § 112, first

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paragraph, with respect to the now claimed invention. Because the instant application does not meet the requirements of 35 U.S.C. § 112, first paragraph, for those reasons given above and it is a continuation of application Serial Number 09/410,603, the prior provisional application does not meet those requirements and, therefore, is unavailable under 35 U.S.C. § 119(e). The effective priority date of the instant application is considered to be the filing date of the parent application 09/410,603, Oct. 10, 1999, because the claimed invention is not supported by either a specific and substantial utility or a well established utility.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 12 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Database SPTREMBL_21, Accession No. O23691, Jan. 1, 1998.

Claims 12 and 18 encompass a polypeptide comprising *an* amino acid sequence of SEQ ID NO: 2, so it is not clear if it is the entire amino acid sequence that is being claimed, or a smaller portion.

Database SPTREMBL_21, Accession No. O23691 discloses an amino acid sequence that is identical to amino acids 51-54, 64-66 and 73-75 of SEQ ID NO: 2. Since *an* amino acid sequence can be interpreted as being as small as two amino acids, Accession No. O23691 meets the limitations of the claims. Claims 13 and 19 are not included in the rejection, since they have

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amino acid sequences flanking those that are identical to the amino acids of SEQ ID NO: 2, and so are not consisting of a sequence of SEQ ID NO: 2.

9. The art considered pertinent to the present application is Database GenEmbl, Accession No. AC005534, Dec. 21, 1999, which discloses a genomic sequence that is 99.5% identical to nucleotides 59-373 of SEQ ID NO: 1 and encodes a polypeptide identical to the polypeptide of SEQ ID NO: 2. This is not considered art over the claimed invention, and is cited as the nucleic acid having the closest homology to the nucleotide sequence of SEQ ID NO: 1.

Conclusion

10. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (703) 308-3312. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached at (703) 308-6564.

Official papers Before Final filed by RightFax should be directed to (703) 872-9306.

Official papers After Final filed by RightFax should be directed to (703) 872-9307.

Official papers filed by fax should be directed to (703) 308-4242.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Eileen B. O'Hara, Ph.D.

A handwritten signature in cursive script that reads "Eileen B. O'Hara".

Patent Examiner